

Application Ser. No.: 10/761,982

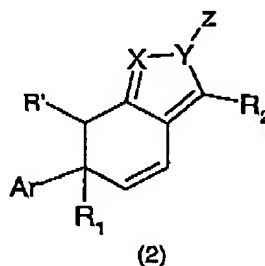
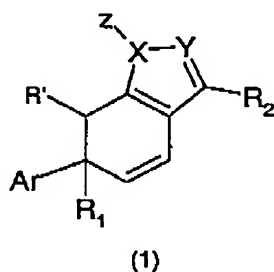
Filing Date: January 21, 2004

Examiner: Stockton, Laura

Amendment Pursuant to 37 C.F.R. § 1.121IN THE CLAIMS:

The claims set forth below with amendments as indicated will replace all prior versions and listing of claims in the application.

1. (Currently amended) A compound of formula (1) or formula (2)



wherein:

X and Y independently are N or CH wherein at least one of X and Y is N;

Ar is:

phenyl optionally substituted with one or more substituents selected from the group consisting of: halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, thio(C₁-C₄)alkyl, NO₂, NH(C₁-C₄)alkyl and N((C₁-C₄)alkyl)₂ wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho carbon of the phenyl wherein said 4 to 6 membered ring may contain a second hetero atom selected from the group consisting of O, S and N, or ~~5- or 6- membered aromatic heterocycle containing one or two hetero atoms selected from the group consisting of O, N and S, and optionally substituted with one or more halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, thio(C₁-C₄)alkyl, NH(C₁-C₄)alkyl, N((C₁-C₄)alkyl)₂~~

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~~wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho carbon of said heterocycle wherein said 4 to 6 membered ring may optionally contain a second hetero atom selected from the group consisting of O, S and N,~~

Z is H, 4-aminophenyl, SO₂R₃ or COR₃ wherein R₃ is (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, Ar as defined above, (C₂-C₆)alkenyl or (C₂-C₆)alkynyl;

R₁ is H, (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl or Ar as defined above;

R' is H or (C₁-C₄)alkyl; and

when Z is H, R₂ is selected from the group consisting of:

cyano,

C(O)-ORa₁ wherein Ra₁ is methyl, ethyl or isopropyl,

C(O)-NHRa₂ wherein Ra₂ is cyclopropyl,

G(O)-N(Ra₂'), wherein N(Ra₂') is aziridiny or azetidiny, optionally substituted with (C₁-C₄)alkyl or Ar as defined above,

C(O)-N(Ra₃)-ORa₃ wherein each Ra₃ may be identical or different and each Ra₃ is independently selected from the group consisting of methyl, ethyl or cyclopropyl,

C(O)Ra₄ wherein Ra₄ is Ar as defined above or (C₃-C₅)cycloalkyl optionally substituted with (C₁-C₄)alkyl or Ar as defined above,

C(Ra₄)=N-Rb wherein:

Ra₄ is H, Ar as defined above, or (C₃-C₅)cycloalkyl optionally substituted with (C₁-C₄)alkyl or Ar as defined above, and

Rb is (C₁-C₂)alkyl, (C₃-C₅)cycloalkyl, hydroxyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyloxy, or (C₁-C₄)alkylenoxy wherein said (C₁-C₄)alkylenoxy optionally may be substituted with halogen or a group selected from the group consisting of carboxyl, (CH₂)_nAr wherein n is 0 or 1 and Ar is as defined above, (C₁-C₄)alkoxy, NH₂, NH(C₁-C₄)alkyl, and N((C₁-C₄)alkyl)₂ wherein said alkyls together with the heteroatom to which they

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are attached may optionally form a 3 to 6 membered ring which may optionally contain a second hetero atom selected from the group consisting of O, S and N,

NH-C(O)R₄ wherein R₄ is H, Ar as defined above, or (C₃-C₅)cycloalkyl optionally substituted with (C₁-C₄)alkyl or Ar as defined above,

NHR₄ wherein R₄ is H, Ar as defined above, or (C₃-C₅)cycloalkyl optionally substituted with (C₁-C₄)alkyl or Ar as defined above,

phenyl, and

5 to 6 membered aromatic heterocycle containing 1 to 3 hetero atoms selected from the group consisting of O, N and S; and

when Z is SO₂R₃ or COR₃, R₂ is carboxyl, NH₂, NH(C₁-C₄)alkyl, N((C₁-C₄)alkyl)₂ or (C₃-C₅)cycloalkylamino; or

a stereoisomeric form of the compound of formula (1) or formula (2), or mixtures of the stereoisomeric forms thereof in any ratio; or

a pharmaceutically pharmaceutically acceptable salt of the compound of formula (1) or formula (2).

2. (Original) The compound according to claim 1 wherein Ar is phenyl, 4-fluorophenyl or 4-methoxyphenyl.

3. (Original) The compound according to claim 2 wherein R₁ is H, (C₁-C₄)alkyl, phenyl or substituted phenyl.

4. (Canceled).

5. (Currently amended) The compound according to ~~claim 4~~ claim 3 wherein R₂ is C(O)-OR₁ and wherein R₁ is ~~(C₁-C₄)alkyl~~ methyl, ethyl or isopropyl.

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6. (Original) The compound according to claim 5 selected from the group consisting of:

ethyl 6,6-diphenyl-6,7-dihydro-2H-indazole-3-carboxylate,
isopropyl 6,6-diphenyl-6,7-dihydro-2H-indazole-3-carboxylate,
methyl 6,6-diphenyl-6,7-dihydro-2H-indazole-3-carboxylate,
ethyl 6-(R,S)-6-methyl-6-phenyl-6,7-dihydro-1H-indazole-3-
carboxylate,
ethyl 6-(+)-6-methyl-6-phenyl-6,7-dihydro-1H-indazole-3-
carboxylate,
ethyl 6-(R,S)-6-phenyl-6,7-dihydro-2H-indazole-3-carboxylate,
ethyl 6-(R)-6-phenyl-6,7-dihydro-2H-indazole-3-carboxylate,
ethyl 6-(S)-6-phenyl-6,7-dihydro-2H-indazole-3-carboxylate,
ethyl 6,6-bis(4-methoxyphenyl)-6,7-dihydro-1H-indazole-3-
carboxylate,
ethyl 6-(R,S)-6-(3,4-dimethoxyphenyl)-6-phenyl-6,7-dihydro-1H-
indazole-3-carboxylate,
ethyl 6-(R,S)-6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazole-
3-carboxylate,
ethyl (-)-6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazole-3-
carboxylate,
ethyl (+)-6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazole-3-
carboxylate,
ethyl 6,6-bis(4-fluorophenyl)-6,7-dihydro-1H-indazole-3-
carboxylate, and
ethyl 7-methyl-6,6-diphenyl-6,7-dihydro-1H-indazole-3-carboxylate.

7. (Currently amended) The compound according to ~~claim 4~~ claim 3 wherein R₂ is CORa₄ and Ra₄ is Ar or (C₃-C₈)cycloalkyl.

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8. (Original) The compound according to claim 7 selected from the group consisting of:

cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone,
cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone,
(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)phenylmethanone,
(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)-(1H-pyrrol-3-yl)methanone,
6-(R,S)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone,
(-)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone,
(+)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone, and
cyclopropyl[6,6-bis(4-fluorophenyl)-6,7-dihydro-1H-indazol-3-yl]methanone.

9. (Currently amended) The compound according to ~~claim 4~~ claim 3 wherein R_2 is $C(O)-NHR_{A2}$, $C(O)-N(R_{A3})-OR_{A3}$ or $C(O)-N(R_{A2}')$.

10. (Original) The compound according to claim 9 selected from the group consisting of:

N-(cyclopropyl)-6,6-diphenyl-6,7-dihydro-1H-indazole-3-carboxamide,
azetidin-1-yl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone,
(N-methoxy-N-methyl)-6,6-diphenyl-6,7-dihydro-1H-indazole-3-carboxamide, and
aziridin-1-yl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone.

11. (Currently amended) The compound according to ~~claim 4~~ claim 3 wherein R_2 is $C(R_{A4})=N-R_b$.

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12. (Original) The compound according to claim 11 selected from the group consisting of:

(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)
methanone oxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)
methanone oxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)
methanone oxime,
(E,Z)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-
yl)methanone oxime,
(E)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone
oxime,
(Z)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone
oxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-2H-indazol-3-
yl)methanone O-methyloxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-2H-indazol-3-yl)methanone
O-methyloxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-2H-indazol-3-yl)methanone
O-methyloxime,
(E,Z)6,6-diphenyl-6,6-dihydro-1H-indazole-3-carbaldehyde O-
methyloxime,
(E, Z)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-
yl)methanone O-allyloxime,
(E)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone
O-allyloxime,
(Z)cyclobutyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone
O-allyloxime,

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(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-allyloxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-allyloxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-allyloxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-methoxyethyl)oxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-methoxyethyl)oxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-methoxyethyl)oxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-benzyloxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-benzyloxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-benzyloxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(4-nitrobenzyl)oxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(4-nitrobenzyl)oxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(4-nitrobenzyl)oxime,
(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-dimethylaminoethyl)oxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-dimethylaminoethyl)oxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-dimethylaminoethyl)oxime,

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(E,Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-fluoroethyl)oxime,
(Z)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-fluoroethyl)oxime,
(E)cyclopropyl(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)methanone O-(2-fluoroethyl)oxime,
(E,Z)-6-(R,S)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(E)-6-(R,S)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(Z)-6-(R,S)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(-)-6-(Z)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(-)-6-(E)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(+)-6-(Z)-cyclopropyl[6-(4-fluorophenyl)-6-phenyl-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(E,Z)cyclopropyl[6,6-bis(4-fluorophenyl)-6,7-dihydro-1H-indazol-3-yl]methanone oxime,
(Z)cyclopropyl[6,6-bis(4-fluorophenyl)-6,7-dihydro-1H-indazol-3-yl]methanone oxime, and
(E)cyclopropyl[6,6-bis(4-fluorophenyl)-6,7-dihydro-1H-indazol-3-yl]methanone oxime.

13. (Currently amended) The compound according to ~~claim 4~~ claim 3 wherein R₂ is NH-C(O)R₄.

14. (Currently amended) The compound according to claim 13 selected from the group consisting of:

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N-(6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl)cyclopropylamide, and
N-[6,6-diphenyl-6,7-dihydro-1H-indazol-3-yl]benzamide.

15. (Currently amended) The compound according to ~~claim 4~~ claim 3 wherein R₂ is Ar phenyl, pyridyl, oxadiazolyl or thiophenyl.

16. (Original) The compound according to claim 15 selected from the group consisting of:

3-(3-methyl[1,2,4]oxadiazol-5-yl)-6,6-diphenyl-6,7-dihydro-1H-indazole,
3,6,6-triphenyl-6,7-dihydro-1H-indazole,
6,6-diphenyl-3-pyrid-3-yl-6,7-dihydro-1H-indazole, and
6,6-diphenyl-3-thiophen-3-yl-6,7-dihydro-1H-indazole.

17. (Currently amended) The compound according to ~~claim 4~~ claim 3 wherein R₂ is CN.

18. (Currently amended) The compound according to ~~claim 14~~ claim 17 wherein the compound is 6,6-diphenyl-6,7-dihydro-1H-indazole-3-carbonitrile.

19. (Original) The compound according to claim 1 wherein Z is SO₂R₃ or COR₃.

20. (Original) The compound according to claim 19 selected from the group consisting of:

6,6-diphenyl-1-(4-toluenesulphonyl)-6,7-dihydro-1H-indazol-3-ylamine and
1-(3-Amino-6,6-diphenyl-6,7-dihydroindazol-1-yl)propenone.

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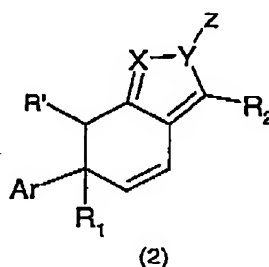
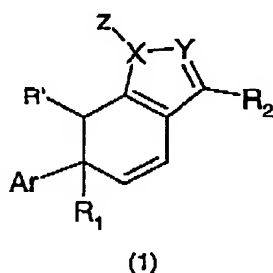
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21. (Original) The compound according to claim 1 wherein Z is 4-aminophenyl.

22. (Original) The compound according to claim 21 wherein the compound is ethyl 1-(4-aminophenyl)-6,6-diphenyl-1H-indazole-3-carboxylate.

23. – 26. (Canceled).

27. (Withdrawn-Currently amended) A method for the treatment of tumors comprising administering to a patient in need of said treatment a therapeutically effective amount of a compound of formula (1) or formula (2)



wherein:

X and Y independently are N or CH wherein ~~at least one of X and Y is N;~~

Ar is:

phenyl optionally substituted with one or more substituents selected from the group consisting of: halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, thio(C₁-C₄)alkyl, NO₂, NH(C₁-C₄)alkyl and N((C₁-C₄)alkyl)₂ wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho carbon of the phenyl wherein said 4 to 6 membered ring may contain a second hetero atom selected from the group consisting of O, S and N, or ~~5 or 6 membered aromatic heterocycle containing one or two hetero atoms selected from the group consisting of O, N and S, and~~

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~~optionally substituted with one or more halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, thio(C₁-C₄)alkyl, NH(C₁-C₄)alkyl, N((C₁-C₄)alkyl)₂ wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho carbon of said heterocycle wherein said 4 to 6 membered ring may optionally contain a second hetero atom selected from the group consisting of O, S and N,~~

Z is H, 4-aminophenyl, SO₂R₃ or COR₃ wherein R₃ is (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, Ar as defined above, (C₂-C₆)alkenyl or (C₂-C₆)alkynyl;

R₁ is H, (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl or Ar as defined above;

R' is H or (C₁-C₄)alkyl; and

when Z is H, R₂ is a selected from the group consisting of:

cyano,

C(O)-ORa₁ wherein Ra₁ is methyl, ethyl or isopropyl,

C(O)-NHRa₂ wherein Ra₂ is cyclopropyl,

C(O)-N(Ra₂'), wherein N(Ra₂') is aziridinyl or azetidiny, optionally substituted with (C₁-C₄)alkyl or Ar as defined above,

C(O)-N(Ra₃)-ORa₃ wherein each Ra₃ may be identical or different and each Ra₃ is independently selected from the group consisting of methyl, ethyl or cyclopropyl,

C(O)Ra₄ wherein Ra₄ is Ar as defined above or (C₃-C₅)cycloalkyl optionally substituted with (C₁-C₄)alkyl or Ar as defined above,

C(Ra₄)=N-Rb wherein:

Ra₄ is H, Ar as defined above, or (C₃-C₅)cycloalkyl optionally substituted with (C₁-C₄)alkyl or Ar as defined above, and

Rb is (C₁-C₂)alkyl, (C₃-C₅)cycloalkyl, hydroxyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyloxy, or (C₁-C₄)alkylenoxy wherein said (C₁-C₄)alkylenoxy optionally may be substituted with halogen or a group selected from the group consisting of carboxyl, (CH₂)_nAr wherein n is 0 or 1 and Ar is as defined above,

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(C₁-C₄)alkoxy, NH₂, NH(C₁-C₄)alkyl, and N((C₁-C₄)alkyl)₂ wherein said alkyls together with the heteroatom to which they are attached may optionally form a 3 to 6 membered ring which may optionally contain a second hetero atom selected from the group consisting of O, S and N,

NH-C(O)Ra₄ wherein Ra₄ is H, Ar as defined above, or (C₃-C₅)cycloalkyl optionally substituted with (C₁-C₄)alkyl or Ar as defined above,

NHRa₄ wherein Ra₄ is H, Ar as defined above, or (C₃-C₅)cycloalkyl optionally substituted with (C₁-C₄)alkyl or Ar as defined above,

phenyl, and

5 to 6 membered aromatic heterocycle containing 1 to 3 hetero atoms selected from the group consisting of O, N and S; and

when Z is SO₂R₃ or COR₃, R₂ is carboxyl, NH₂, NH(C₁-C₄)alkyl, N((C₁-C₄)alkyl)₂ or (C₃-C₅)cycloalkylamino; or

a stereoisomeric form of the compound of formula (1) or formula (2), or mixtures of the stereoisomeric forms thereof in any ratio; or

a ~~pharmaceutically~~ pharmaceutically acceptable salt of the compound of formula (1) or formula (2).

28. (Withdrawn) The method of claim 27 wherein the therapeutically effective amount comprises an amount sufficient to inhibit microtubule polymerization.

29. (Withdrawn) The method of claim 27 wherein the therapeutically effective amount comprises a therapeutically effective endothelial cell detaching amount.

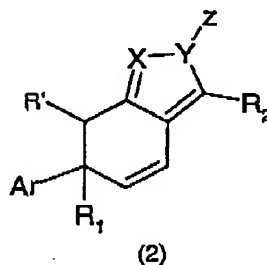
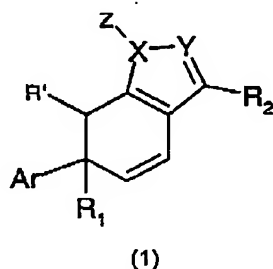
30. (Withdrawn) The method of claim 27 wherein the therapeutically effective amount comprises an amount sufficient to inhibit vascularization of said tumors.

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31. (Withdrawn-Currently amended) A method for the treatment of cancerous cells comprising administering to a patient in need of said treatment a therapeutically effective amount of a compound of formula (1) or formula (2)



wherein:

X and Y independently are N or CH wherein at least one of X and Y is N;

Ar is:

phenyl optionally substituted with one or more substituents selected from the group consisting of: halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, thio(C₁-C₄)alkyl, NO₂, NH(C₁-C₄)alkyl and N((C₁-C₄)alkyl)₂ wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho carbon of the phenyl wherein said 4 to 6 membered ring may contain a second hetero atom selected from the group consisting of O, S and N, or ~~5 or 6 membered aromatic heterocycle containing one or two hetero atoms selected from the group consisting of O, N and S, and optionally substituted with one or more halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, thio(C₁-C₄)alkyl, NH(C₁-C₄)alkyl, N((C₁-C₄)alkyl)₂ wherein said alkyl may optionally form a 4 to 6 membered ring together with the heteroatom to which it is attached and an ortho carbon of said heterocycle wherein said 4 to 6 membered ring may optionally contain a second hetero atom selected from the group consisting of O, S and N,~~

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Z is H, 4-aminophenyl, SO_2R_3 or COR_3 wherein R_3 is $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, Ar as defined above, $(\text{C}_2\text{-C}_6)\text{alkenyl}$ or $(\text{C}_2\text{-C}_6)\text{alkynyl}$;

R_1 is H, $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$ or Ar as defined above;

R' is H or $(\text{C}_1\text{-C}_4)\text{alkyl}$; and

when Z is H, R_2 is a selected from the group consisting of:

cyano,

$\text{C}(\text{O})\text{-ORa}_1$ wherein Ra_1 is methyl, ethyl or isopropyl,

$\text{C}(\text{O})\text{-NHRa}_2$ wherein Ra_2 is cyclopropyl,

$\text{C}(\text{O})\text{-N}(\text{Ra}_2')$, wherein $\text{N}(\text{Ra}_2')$ is aziridinyl or azetidiny, optionally substituted with $(\text{C}_1\text{-C}_4)\text{alkyl}$ or Ar as defined above,

$\text{C}(\text{O})\text{-N}(\text{Ra}_3)\text{-ORa}_3$ wherein each Ra_3 may be identical or different and each Ra_3 is independently selected from the group consisting of methyl, ethyl or cyclopropyl,

$\text{C}(\text{O})\text{Ra}_4$ wherein Ra_4 is Ar as defined above or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$ optionally substituted with $(\text{C}_1\text{-C}_4)\text{alkyl}$ or Ar as defined above,

$\text{C}(\text{Ra}_4)\text{=N-Rb}$ wherein:

Ra_4 is H, Ar as defined above, or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$ optionally substituted with $(\text{C}_1\text{-C}_4)\text{alkyl}$ or Ar as defined above, and

Rb is $(\text{C}_1\text{-C}_2)\text{alkyl}$, $(\text{C}_3\text{-C}_5)\text{cycloalkyl}$, hydroxyl, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $(\text{C}_2\text{-C}_4)\text{alkenyloxy}$, or $(\text{C}_1\text{-C}_4)\text{alkylenoxy}$ wherein said $(\text{C}_1\text{-C}_4)\text{alkylenoxy}$ optionally may be substituted with halogen or a group selected from the group consisting of carboxyl, $(\text{CH}_2)_n\text{Ar}$ wherein n is 0 or 1 and Ar is as defined above, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, NH_2 , $\text{NH}(\text{C}_1\text{-C}_4)\text{alkyl}$, and $\text{N}((\text{C}_1\text{-C}_4)\text{alkyl})_2$ wherein said alkyls together with the heteroatom to which they are attached may optionally form a 3 to 6 membered ring which may optionally contain a second hetero atom selected from the group consisting of O, S and N,

$\text{NH-C}(\text{O})\text{Ra}_4$ wherein Ra_4 is H, Ar as defined above, or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$ optionally substituted with $(\text{C}_1\text{-C}_4)\text{alkyl}$ or Ar as defined above,

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NHRa₄ wherein Ra₄ is H, Ar as defined above, or (C₃-C₅)cycloalkyl optionally substituted with (C₁-C₄)alkyl or Ar as defined above, phenyl, and

5 to 6 membered aromatic heterocycle containing 1 to 3 hetero atoms selected from the group consisting of O, N and S; and

when Z is SO₂R₃ or COR₃, R₂ is carboxyl, NH₂, NH(C₁-C₄)alkyl, N((C₁-C₄)alkyl)₂ or (C₃-C₅)cycloalkylamino; or

a stereoisomeric form of the compound of formula (1) or formula (2), or mixtures of the stereoisomeric forms thereof in any ratio; or

a ~~pharmacetically~~ pharmaceutically acceptable salt of the compound of formula (1) or formula (2).

32. (withdrawn) The method of claim 31 wherein the therapeutically effective amount comprises an amount sufficient to inhibit microtubule polymerization.

33. (Withdrawn) The method of claim 31 wherein the therapeutically effective amount comprises a therapeutically effective endothelial cell detaching amount.

34. (Withdrawn) The method of claim 31 wherein the therapeutically effective amount comprises an amount sufficient to inhibit vascularization of said cancerous cells.

35. (Original) A pharmaceutical composition comprising one or more compounds of formula (1) or formula (2) according to claim 1 and one or more pharmaceutically acceptable carriers, diluents, adjuvants or excipients.